Risk assessment of ritual use of oral dimethyltryptamine (DMT) and harmala alkaloids

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ABSTRACT

Aim   To extend previous reviews by assessing the acute systemic toxicity and psychological hazards of a dimethyltryptamine and β-carboline brew (ayahuasca/hoasca) used in religious ceremonies. **Method**   A systematic literature search, supplemented by interviews with ceremony participants. **Results**   No laboratory animal models were located that tested the acute toxicity or the abuse potential of ayahuasca. Separate animal studies of the median lethal dose of dimethyltryptamine (DMT) and of several harmala alkaloids indicated that a lethal dose of these substances in humans is probably greater than 20 times the typical ceremonial dose. Adverse health effects may occur from casual use of ayahuasca, particularly when serotonergic substances are used in conjunction. DMT is capable of inducing aversive psychological reactions or transient psychotic episodes that resolve spontaneously in a few hours. There was no evidence that ayahuasca has substantial or persistent abuse potential. Long-term psychological benefits have been documented when ayahuasca is used in a well-established social context. **Conclusion**   A decoction of DMT and harmala alkaloids used in religious ceremonies has a safety margin comparable to codeine, mescaline or methadone. The dependence potential of oral DMT and the risk of sustained psychological disturbance are minimal.

Keywords   Abuse potential, ayahuasca, dimethyltryptamine, DMT, toxicity.

INTRODUCTION

Among substances suspected of having abuse potential, N,N-dimethyltryptamine (DMT) has received relatively little attention. However, in 2006, a case was decided by the US Supreme Court that involved the question as to whether a DMT and β-carboline plant decoction (ayahuasca/hoasca) is safe for ceremonial use by members of a small spiritualist Christian church [1]. The church prevailed in a unanimous decision in part because the government, which opposed the use of DMT, could not meet its burden of showing that hoasca posed a serious health risk to church members. This paper is a review of the known acute systemic risks of oral DMT and concomitantly ingested harmala alkaloids.

Risk refers to the quantified probability of a future harm. The concept of risk requires a causal relationship between a hazard (such as a drug overdose) and a known unfavorable outcome (such as illness or death). In order to establish this causal relationship, a stimulus must produce an effect more often than would normally occur in the absence of that stimulus. Thus, the probabilistic estimate of risk is often an intrinsic aspect of the research process by which a causal relation is demonstrated. In the case of oral DMT, probabilistic estimates can be made for very few of the drug's effects at the present time. Some effects, both favorable and unfavorable, that have been attributed to DMT may amount to little more than plausible associations. Given the limited amount of published scientific data regarding oral DMT, this paper takes a broad view of potential hazards with the expectation that future research will better establish the risks that might actually exist.

Ayahuasca (EYE-ah-WAS-ka) or hoasca (WAS-ka) is a mixture consisting essentially of two compounds. One is an amine—the simplest and most common being the tryptamine DMT. The second compound is a monoamine oxidase inhibitor (MAOI) in the form of a β-carboline such as harmine, harmaline or tetrahydroharmine. DMT alone has predicable and significant psychological

activity when smoked, injected or insufflated; but when used orally it only becomes, or remains, psychoactive in combination with an MAOI [2–4].

Ayahuasca/hoasca is prepared customarily by combining the leaves from the *Psychotria viridis* bush along with bark scraped from the stem of the *Banisteriopsis caapi* vine [4,5]. The ingredients are boiled for several hours and then decanted. The resulting thick, brown, oily liquid (referred to colloquially in some locales as 'vine of the souls' or 'vine of the dead') has been used throughout the Amazon Basin as a medicinal and ceremonial beverage since antiquity [6].

Various sacramental brews containing DMT and β-carbolines, used primarily in Amazonia, are generally known as ayahuasca. The term 'hoasca', a Portuguese transliteration of ayahuasca, is limited historically and properly to a subclass of ayahuasca beverages associated with a specific sacramental use ([5], chapter 16, 'Hoasca versus Ayahuasca'). The most commonly recognized sacramental use of ayahuasca occurs among members of two churches in Brazil: the O Centro Espirita Beneficiente Uniao Do Vegetal (UDV), founded in 1961 with approximately 8000 current members, and the Santo Daime, founded around 1940 with approximately 2500 current members. Hoasca preparation occurs as part of a religious ritual known as *preparo* in the UDV. The Santo Daime church also uses a decoction of *P. viridis* and *B. cappi* called *santo daime* or simply *daime*, and its preparation ritual is known as *feitio* [7]. In the present paper, 'hoasca' will refer exclusively to UDV's sacramental decoction of plant DMT and harmala alkaloids.

The UDV cultivates the plants that are used in their hoasca 'tea' on land that the church owns and maintains for that purpose. The preparo ceremony can involve up to 200 people working together at a UDV temple over a period of several days. Photographs of the process appear in Metzner ([8], pp. 20, 21, 205). In 1992, the Brazilian Federal Narcotics Council granted legal status for the use of hoasca in religious contexts.

METHOD

The present paper extends previous reviews [9,10] that compared the acute lethal toxicity and the abuse potential of various psychoactive substances. A simple inductive and iterative procedure was used to locate English-language serial publications, from 1969 to 2005, accessible through six databases: Biosis Previews, Digital Dissertations, Google, PsychAbstracts, Pubmed and Toxline. The Science Citation Index was occasionally used to follow-up unusually salient reports. Six primary search terms—'ayahuasca', 'hoasca', 'dimethyltryptamine', 'harmine', 'harmaline' and 'tetrahydroharmine'—were keyed into the search engines and scanned for the topics

'overdose', 'lethal dose', 'lethality', 'toxicity', 'death', 'therapeutic index', 'abuse potential' and 'dependency'. The most relevant books, reference works and special journal issues (e.g. [5,8,11–12]) were also consulted, thus expanding the information sources beyond those located only by the search descriptors. In 2003, this author met with 16 people 2 hours before and periodically for 12 hours after an ayahuasca ceremony led by a Peruvian shaman. In 2005, the author had access to a detailed legal document [13] consisting of more than 1000 pages that served as the evidentiary basis for health information about hoasca for use in the US Supreme Court case mentioned previously [1].

An item retrieved during the literature search was considered potentially relevant if it met at least two of four criteria: (1) DMT or one of the monoamine oxidase inhibitors was quantified with respect to an effective or a toxic dose; (2) the health status of the individual was indicated; (3) the possible use of concomitant substances was mentioned; and (4) the data source appeared to be technical or scholarly in nature.

RESULTS

Fewer than 100 scholarly articles that focused specifically on ayahuasca/hoasca were located in English-language serial publications. The majority of these articles involved inapplicable topics such as neurological experiments, ethnographic descriptions or potential medical uses. The descriptors 'dimethyltryptamine', 'harmine', 'harmaline' and 'tetrahydroharmine' resulted in approximately 200 citations retrieved from the databases, excluding Google and the Science Citation Index. However, after cross-indexing the keyword 'toxicity' with these four descriptors, the number of non-redundant citations that met the screening criteria was fewer than 25. When all relevant citations from serial publications were supplemented with excerpts from scholarly books, monographs and published reports, the total number of documents printed and filed was approximately 140.

Description of ayahuasca/hoasca brew

The DMT alkaloid has been reported as ranging from 0.1% to 0.66% dry weight in *P. viridis* leaves [14]. Surprisingly, the DMT in leaf samples from a single *P. viridis* plant has been shown to vary from approximately 3 mg/g to 9.5 mg/g dry weight in the course of one day. The concentrations of the β-carboline alkaloids in *B. caapi* have been reported as ranging from 0.05% to 1.95% dry weight [15,16].

Substantial variation in concentrations and proportions of the constituents of ayahuasca brews can be expected as a consequence of the varying chemical

Table 1 Quantity (in milligrams) of alkaloids in ayahuasca/hoasca brews.[1]

Dose size [2]	DMT	Harmine	Harmaline	THH	Reference
140 ml	35.6	238	28	150	[2,14,18]
237 ml	33	17	26	Not stated	[75]
60 ml	36	280	25	96	[15]
Gelatin capsule	30	120	None	None	[4]
100 ml	9.1	47.5	Trace	4.2	[17]
100 ml[3]	8.8	9.2	Not stated	26.5	[17]
Gelatin capsule	42	71	4.8	57	[30]
200 ml	25	30	trace	10	[16]

[1]Adapted, in part, from Riba [76]. [2]Estimated average given to a 70 kg adult in the study referenced. [3]Two samples of ayahuasca reported in the same study.

composition of the source plants as well as different methods of preparation. Average DMT doses in assayed ayahuasca brews have ranged from 8.8 mg [17] to 42 mg [18]. The content of other alkaloids also varied widely (see Table 1). This fivefold variance of DMT quantities in ayahuasca brews might be compared to the common fivefold variance in caffeinated beverages which range typically from 0.2 mg/ml of caffeine in green tea to 1.0 mg/ml of caffeine in filtered coffee [19].

The ritual structure in which hoasca is ingested provides some control of dosage and subsequent psychological effects. Because the natural sources used in preparation of the tea does not allow UDV members to standardize their hoasca brew with respect to DMT or β-carbolines, the person conducting the ceremony drinks the brew before administering it to UDV members as a means of testing for potency. Different amounts of the brew are initially offered to individual participants and, depending upon reactions, a participant may be offered a second cup at his or her request.

A clear distinction must be made between preparations consisting exclusively of DMT that are injected, smoked or insufflated versus DMT preparations that are oral mixtures of DMT and MAOI. Injected, smoked or insufflated DMT is noted for its very rapid activity. Peak cognitive effects last only 3–10 minutes, and normal consciousness returns within 30 minutes. In contrast, initial somatic effects (e.g. nausea, tingling, increased body temperature) after ingesting oral DMT appear in approximately 20 minutes, followed by the onset of cognitive effects that peak between 60 and 120 minutes [20]. The cognitive effects diminish gradually to a normal state in approximately 4 hours. At normally used doses, the psychological effects of oral DMT are less intense than those of injected, smoked or insufflated DMT.

Acute lethality

A traditional and standard criterion for assessing the relative toxicity of various substances has been the lethal dose of a substance. The median lethal dose (LD_{50}) is the statistically derived quantity of a substance given in a single dose that causes death in 50% of the experimental animals. One early study by Trevan [21] used more than 900 mice to assess the toxicity of cocaine and of insulin. More humane standards, such as the minimal lethal dose or the maximal non-lethal dose, are being gradually implemented by toxicologists, although many regulatory agencies still rely on the traditional LD_{50}. Some test procedures have been advocated that can reduce the number of killed animals to as few as six [22].

The criterion of single-dose acute lethality is an extremely limited estimate of human toxicity because it does not take into account variables such as interspecies differences, repeated dosing, environmental conditions, prior health status and psychological factors. None the less, the influence that such variables might have on an established dose–response relationship should not obscure the fact that the LD_{50} is a clearly defined, replicable and important benchmark of toxicity.

The LD_{50} of DMT in mice is reported as 47 mg/kg intraperitoneally and 32 mg/kg intravenously [23]. No other LD_{50} data on DMT are believed to be available in the English language at this time. Five compounds with structural resemblance to DMT—serotonin, psilocin, psilocybin, bufotenin and 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT)—all have an intravenous LD_{50} among rodents that are similar to, or substantially less toxic than, DMT. In two rare studies reporting oral lethal doses of these related compounds, the LD_{50} of serotonin in mice was 60 mg/kg [23]; the LD_{50} of 5-MeO-DMT in mice was 278 mg/kg [24].

The principal β-carboline alkaloids added to DMT in ayahuasca mixtures are harmine, harmaline and tetrahydroharmine. In addition to the *B. caapi* vine, these alkaloids can be found in the *Peganum harmala* (Syrian rue) shrub, a desert plant native to Central Asia. An aqueous extract of *P. harmala* seeds administered orally to rats resulted in a LD_{50} of 2 g/kg [25]. Because the β-carboline admixtures in ayahuasca appear to be less

Table 2 Heart rate and blood pressure increases after administration of DMT or other psychoactive substances.

Substance	Dose (mg/kg)[1]	Peak interval	Heart rate (bpm)	Systolic (mmHg)	Diastolic (mmHg)	Reference[2]
DMT						
Intravenous	0.4	2 minutes	26	35	30	[27][2]
Oral	0.48	20 minutes	7.4	9.0	9.3	[3]
Oral	0.5	45 minutes	6.4	8.8	10.4	[20]
Oral	0.75	45 minutes	8.0	13.4	9.8	[20]
Oral	1.0	45 minutes	9.2	13.8	8.6	[20]
Alcohol oral	1157	15 minutes	9	−2	1	[77]
Caffeine oral[3]	3.3	15 minutes	4.0	5.0	5.0	[29]
Cocaine insufflated[4]	1.37	55 minutes	17	14	14	[78]
Marijuana smoked	(98.6 ng/ml)[5]	15 minutes	11.6	(See footnote 6)		[79]
MDMA oral	1.5	60 min	28	25	7	[80]

[1]Assumes an individual who has not developed tolerance to the indicated substance. [2]The reference listed is the primary, but not the exclusive, source for the data summarized in the table. Some original data were averaged. [3]Caffeine powder mixed with grapefruit juice; caffeine dose was equivalent to two or three cups of instant coffee. [4]Administered as 120 mg of white powder (cocaine and lactose) in four 'lines', snorted two lines per nostril. [5]Plasma THC from 10 puffs, at 1-minute intervals, from a marijuana cigarette containing 1.75% THC. [6]Typically, a slight increase in blood pressure when in a supine position, a decrease when in an upright position.

toxic than DMT, our attention should focus on the DMT component.

A simple extrapolation of DMT lethality data from mice to humans is obviously untenable. We are therefore forced to make some intrepid, but not original, assumptions. One traditional rule for scaling unknown differences between humans and non-human animal species is simply to assume that humans are 10 times more sensitive, based on body weight, than rodents [26]. To be even more cautious in light of the absence of LD_{50} data regarding oral DMT, let us assume that humans are 20 times more sensitive than rodents. This would result in a human LD_{50} of 1.6 mg/kg for DMT administered intravenously, or a total intravenous dose of 112 mg for a typical 70 kg person. Because we are interested in the potential toxicity of oral DMT in ayahuasca, it is necessary to convert our estimated intravenous LD_{50} dose of 1.6 mg/kg DMT to an oral equivalent. Usually, an intravenously administered dose of a substance is assumed to have bioavailability of 100%. The bioavailability of an oral dose is significantly less. An oral DMT dose of 1.0 mg/kg has been reported to increase blood pressure and heart rate comparable to a 0.1–0.2 mg/kg intravenous dose [20]. With respect to psychological reactions, an intravenous DMT bolus of 0.4 mg/kg has been documented carefully as 'highly psychedelic' ([12], p. 138), while an oral dose of DMT 'in excess of 2.0 mg/kg' in ayahuasca is known to produce maximal effects ([4], p. 175). Let us assume an intravenous-to-oral conversion factor of 1 : 5, based on the assumption that 0.4 mg intravenously is equivalent to approximately 2.0 mg of oral DMT. If 1.6 mg/kg is a median lethal dose of intravenous DMT, then a median lethal dose of oral DMT would be 8 mg/kg, or a total dose of 560 mg for a 70 kg individual. Note, however, that 560 mg is the estimated median dose, and therefore one-half of potential DMT fatalities would occur at an oral dose less than 560 mg.

A safety ratio or safety margin for ayahuasca can be estimated by comparing the calculated LD_{50} to the customary effective dose. The average ceremonial dose of DMT, as listed in Table 1, is about 27 mg; therefore, the safety margin for ayahuasca is approximately 20 (560/ 27 = 20.7).

Cardiac stress

Intravenous DMT is known to increase heart rate rapidly, as well as systolic and diastolic blood pressure. Strassman & Qualls [27] reported that a 0.4 mg/kg dose of DMT at the postinjection interval of 2 minutes raised the heart rate approximately 26 beats per minute (bpm), and raised systolic pressure by 35 mmHg and diastolic pressure by 30 mmHg. DMT plus β-carbolines in ayahuasca ingested in doses ranging from 0.48 mg/kg to 1.0 mg/kg were shown to induce peak increases in heart rate and blood pressure at about one-third that of intravenous DMT after 90 and 120 minutes [3,20]. Table 2 summarizes these data along with comparisons of some commonly used psychoactive substances. The reference cited for each of the substances in Table 2 is the primary, but not exclusive, source of the information presented.

On the basis of acute heart rate and blood pressure data, the hemodynamic effects of a typical dose of ayahuasca appear to be less potentially hazardous than many commonly used psychoactive substances. This tentative conclusion assumes that any substance listed in

Table 2 is administered once by the route and in the quantity indicated without any concomitant pharmacologically active substances. Occasional stroke, myocardial infarction and other adverse cardiovascular events can be expected to be associated with, even if not directly caused by, the use of ayahuasca or other drugs or foods that induce acute hemodynamic changes. Individual differences in metabolism and health status often result in a wide range of reactions to psychoactive substances. For example, the heart rate of some of the participants in the Strassman & Qualls intravenous DMT study [27] peaked at 150 bpm, while the heart rate of other participants was raised no higher than 95 bpm. Furthermore, the hemodynamic reaction to ayahuasca may depend on the relative concentrations of DMT to the β-carbolines. In decoctions tested by Pomilio, Vitale & Ciprian-Ollivier [17], an exceptionally low concentration of DMT compared to β-carbolines significantly decreased heart rate. An experiment with dogs found that harmala alkaloids decreased heart rate but were inconsistent in their effect on blood pressure [28].

Because heart rate increases with ayahuasca are so minimal, the differences may be the result of unrelated physical activity of the participants. Such changes might be put into perspective by a study conducted by Hartley, Lovallo & Whitselt [29]. A beverage containing a 230 mg dose of caffeine (equivalent to two or three 150 ml cups of instant coffee) resulted in only negligible increases in heart rate (4 bpm) and blood pressure (5 mmHg). Later in the same study, the researchers asked the 77 study participants to deliver a 3-minute speech 'to a video camera in front of 2 experimenters wearing white coats' ([29], p. 1023). Under this anxiety-producing condition, the average increase in heart rate was 30 bpm; the systolic pressure increased an average of 28 mmHg and the diastolic pressure increased an average of 21 mmHg. These increases are more than twice those occurring with oral DMT.

It is generally held that the β-carbolines in ayahuasca are reversible and highly selective inhibitors of MAO [30]. The ayahuasca-induced blockade of MAO presumably allows a larger quantity of serotonin to accumulate in nerve terminals. Excessive accumulation can produce a range of adverse physiological symptoms, a 'serotonin syndrome', that includes tremor, diarrhea, autonomic instability, hyperthermia, sweating, muscle spasms and possible death [31].

A few irreversible or non-selective MAO inhibitors (e.g. phenelzine, tranylcypromine) are associated strongly with instances of severe serotonin syndrome, but a large number of opiates, analgesics, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) and anti-migraine agents have also been implicated [31]. Individuals who have recently used ginseng, St John's wort, dextromethorphan or 3,4-methylenedioxymethamphetamine (MDMA: ecstasy) should be cautious about using ayahuasca. Physical discomfort or chronic pain (e.g. backache) may be exacerbated by ayahuasca, so potential users should be warned of this side effect.

Table 3 lists six reported instances in which there were severe toxic reactions to a psychoactive tryptamine and/or a β-carboline. The death of a 25-year-old male caused by amine intoxication [32] involved 5-MeO-DMT in addition to DMT and β-carboline. No laboratory animal studies were located during the present review that compared the toxicity of orally active 5-MeO-DMT with orally active DMT. However, 5-MeO-DMT is reported to be more potent than DMT when smoked [5] or taken orally with harmaline [4]. Experienced researchers have cautioned that these substances should not be casually interchanged in ayahuasca-like preparations. The male decedent ingested an unknown quantity of 'herbal tonics' that presumably contained MAOIs in addition to the DMT and 5MeO-DMT because he was found to have a blood concentration of tetrahydroharmine three times higher than that found among 14 volunteers in a UDV hoasca study [2]. The autopsy was performed the day after the body was discovered, so post-mortem drug redistribution makes it difficult to determine what the peak cardiac or peripheral blood concentration of tetrahydroharmine or 5-MeO-DMT might have actually been.

The briefly described fatality of a 71-year-old diabetic female, listed in Table 3, reported that only tobacco leaves and *B. caapi* were the constituents of the so-called 'ayahuasca' brew [33]. The abstract did not document the concentration of any β-carbolines, but did report measurements (at unstated time intervals) of 1900 ng/ml and 710 ng/ml of blood nicotine. These concentrations exceed by at least 20 times the average post-mortem nicotine concentration (34 ng/ml) reported by Ekwald & Clemedson [34]. 'The cause of death [of the 71-year-old] was attributed to acute nicotine intoxication' ([33], p. 287). Administration of the unorthodox nicotine/β-carboline brew by enema to this older person, who was a non-smoker, precludes the relevance of this case to typical ayahuasca/hoasca use.

The quantity of *P. harma* seeds consumed as a single intoxicant by the two individuals cited in Table 3 [36,37] should be distinguished from the lower quantity of *B. caapi* or *P. harmala* that is used customarily in an ayahuasca brew. These individuals ingested 15–50 times more β-carboline alkaloids than the 3 g needed to maintain the oral activity of DMT in an ayahuasca preparation [5]. Herraiz [38] has noted that coffee may act as a MAOI, and the caffeine used by one of the decedents probably intensified the effect of the harmala seeds.

Table 3 Acute toxic reactions to ayahuasca-related compounds.

Age/sex	Primary	Estimated	Effects	Toxicological	Factors	Reference
25 M	5-MeO-DMT	Unknown quantity of 'herbal tonics'	Death caused by 'amine intoxication'	5-Meo-DMT 1.88 mg/l, THH 0.38 mg/l, harmine 0.17 mg/l	Camping in park, autopsy examination unremarkable	[32]
71 F	Ayahuasca brew	Not reported	Death caused by 'nicotine intoxication'	Nicotine 1900 mg/l and 710 mg/l	Non-smoker, no emesis, brew administered by enema	[33]
36 M	Ayahuasca brew	100 ml of brew	Gross motor tremors, confusion, symptoms resolved without treatment after 4 hours	No blood chemistry reported	Daily use of 20 mg of oral fluoxetine	[35]
35 M	*Peganum harmala*	150 g of *P. harmala* seeds	Heart rate 100 bpm, bp 80/40 mmHg, convulsion, stable in few hours after infusion NaCl/glucose solution	β-carbolines not reported	Gastric ulcer, mild anemia but other parameters normal	[36]
27 F	*P. harmala*	50 g of *P. harmala* seeds	Hallucinations, GI disturbance, bradycardia, resolved in a few hours	β-carbolines, caffeine level not reported	Seeds ingested with coffee[1]	[37]
20–50[2]	Harmine, atropine scopolamine	A brew of harmine 27 mg, atropine 4 mg, scopolamine 78 mg	Tachycardia, coma, amnesia, hallucination, all patients recovered with supportive treatment	Harmine 179 mg/l, atropine 27 mg/l scopolamine 515 mg/l	Ingested alkaloids had 'synergistic actions'	[39]

[1]Coffee brews contain β-carboline alkaloids. [2]'More than 30 people aged 20–50 years'. No information provided regarding sex or health status of patients.

The last item listed in Table 3 involved more than 30 individuals between the ages of 20 and 50 years who 'were participating in a meditation session named "releasing autohypnosis of forest medicine men"' ([39], p. 50). The published report does not detail the number of participants who were hospitalized, their gender or their health status following the ingestion of 100–200 ml of herbal tea, although all the patients recovered satisfactorily. Fatalities from atropine or scopolamine are rare, and from harmine are extremely rare. The reported dose of atropine (4 mg) and of scopolamine (78 mg) received by the meditation session participants is eight to 13 times less than the estimated minimal lethal dose of these substances [40,41]. The severe reactions of at least a few of the individuals who required mechanical ventilation was attributed by the report authors to the combined synergistic actions of harmine, atropine and scopolamine. This incident provides additional evidence of the potential danger of combining pharmacologically active substances in non-traditional ways.

To this author's knowledge, there have been no deaths caused by hoasca or any other traditional DMT/β-carboline ayahuasca brews. The probability of a toxic overdose of ayahuasca is seemingly minimized by serotonin's stimulation of the vagus nerve which, in turn, induces emesis near the level of an effective ayahuasca dose. The risk of overdose appears to be related primarily to the concurrent or prior use of an additional serotonergic substance. People who have an abnormal metabolism or a compromised health status are obviously at a greater risk than the normal population, and might prudently avoid the use of ayahuasca preparations.

Psychological dysfunction

The general sequence of psychological and cognitive responses to ayahuasca is dose-dependent and predictable; however, the reactions of any particular individual at any one session are not. With a medium dose of DMT, objects in the environment appear to vibrate and increase in brightness. Rapidly moving patterns and scenes emerge that are visible with eyes either open or closed. This experience is referred to as being a 'visionary state' ([42], p. 109). It should be noted that these altered perceptions and cognitions do not usually cause users to become unaware of their surroundings or lose the ability to speak coherently. Many users walk to the restroom as a result of diarrhea.

Riba and colleagues [20] described the reactions of six volunteers after they each received doses of 0.05, 0.75 and 01.0 mg/kg of ayahuasca. Results obtained on Addiction Research Center Inventory (ARCI) scales showed that as the doses increased, emotions of happiness, sadness, awe and amazement also increased. At medium and high doses, the volunteers agreed that the experience seemed similar to a dream and that the sense of self and the passing of time were deeply affected. For example, the awareness between individuals can become so interlinked that typical self-centered judgements about the contents of another person's statement are simply absent. With respect to time perception, some people report that during an ayahuasca session they are swept into a conscious state where the usual orderly progression of time becomes obviously non-existent, and they experience 'eternity' ([43], p. 45). This sensation/perception was often associated with the emotion of well-being, but it can also be accompanied by feelings of terror. Virtually all data sources indicate that the DMT or ayahuasca experience has a substantial degree of unpredictability with respect to both aversive and positive aspects, depending on variables such as dosage, participant's intention and setting. Reactions during ayahuasca ceremonies have ranged from profound calmness [44] to anguished cries for forgiveness [45].

In interviews with 150 informants, Shannon [46] reported that, even among individuals without academic education or philosophical training, the ayahuasca experience prompted users to reflect seriously on the phenomena of life, nature and human consciousness. A pilot study by Grob and colleagues [47] comparing 15 members of the UDV with a control group of 15 non-members revealed that the UDV members showed more rigidity, regimentation, reflection and word-recall on various tests than non-members. According to Grob ([47], p. 90), 'all of the 15 UDV subjects claimed that their experience with ritual use of hoasca as a psychoactive ritual sacrament had had a profound [positive] impact on the course of their lives'. Most of the UDV members had a history of moderate to severe alcohol use prior to joining the UDV. This variable was not reported for the control group, so the generalization of this study's result to the general population is uncertain.

Certain perceptual characteristics of the ayahuasca experience overlap those of schizophrenia, and a few researchers have reported that urinary or blood levels of DMT are above normal in schizophrenic individuals [48,49]. This has led to the hypothesis that the non-destruction of dimethylated indolealkylamines such as DMT could play a role in progressive deterioration of cognitive processes [50]. Other studies have produced conflicting results and alternative conclusions [51,52]. Jacob & Presti ([53], p. 935) proposed that increased DMT, acting at the G-protein-coupled trace amine receptor, might actually serve in schizophrenics as 'a homeostatic response to calm or suppress psychotic activity, rather than exacerbate it'. At present, the proposition that endogenous DMT in schizophrenia is related biochemically to ayahuasca-induced states of consciousness remains a speculative hypothesis.

The hallucinogenic effect of ayahuasca and other tryptamine derivatives can precipitate severe adverse psychological reactions, and this is especially true when administered outside established ceremonial practices [54]. For example, two cases of unsupervised use of 5-methoxy-N,N-diisopropyltryptamine (5-MeO-DIPT, 'foxy') have been reported in which an unknown amount of 5-MeO-DIPT caused sensory hallucinations requiring several hours of hospitalization [55,56]. Transient psychotic episodes are also known to occur with high doses of psilocybin [57] and LSD [58]. LSD, psilocybin and 5-MeO-DIPT are, however, orally active and more potent than DMT; thus the comparability of these three substances with DMT is somewhat problematic.

Over a period of 5 years, the medical studies section of the UDV documented between 13 and 24 cases in which ayahuasca might have been a contributing factor in a psychotic incident ([13], p. 701). The incidents documented by the UDV occurred from an estimated total of 25 000 servings of the hoasca tea. Although the prevalence rate of psychosis or schizophrenia among adults in the United States varies according to the way in which diagnostic criteria are applied, the generally accepted estimate is approximately 1.3% [59]. A reported UDV rate of psychotic episodes under 1% suggests that the use of hoasca is not a triggering event for sustained psychosis. Many or most of the UDV psychotic episodes were transient in nature and resolved spontaneously ([13], p. 623).

Dependence and abuse potential

The extent to which ayahuasca might lead to physiological dependence or compulsive drug-seeking is an

important public health concern. The physiological dependence potential of DMT and ayahuasca remains to be documented convincingly. Hallucinogenic substances structurally similar to DMT are rarely used in a compulsive manner that would meet the dependence criteria of the *Diagnostic and Statistical Manual* version IV (DSM-IV) [60]. No studies were located during the present review that reported that the termination of DMT resulted in an abstinence syndrome.

With respect to drug tolerance, however, a few non-human animal studies have been conducted that show varying degrees of tolerance to behavioral and physiological responses over a period of 3 or 4 weeks [61–63]. Little or no tolerance to emotional or autonomic effects was reported in one study, where human volunteers were administered DMT four times at 30-minute intervals [64], and in another study where DMT was administered twice daily for 5 days [52].

Despite the presumed absence of physiological dependency and tolerance, ayahuasca might, nonetheless, function as a positive reinforcer leading to significant abuse potential. We would want to know, for example, what proportion of individuals who try DMT or ayahuasca once or twice fall into a pattern of chronic use that they then find difficult to quit. The UDV has reported that 15–20% of first-time participants in hoasca ceremonies become UDV members ([13], p. 700). This subsequent participation in the UDV church is within the reported range of first-time visitors who become members of Christian churches in the United States [65].

Future consumption patterns of ayahuasca are difficult of determine because, in part, the frequency of present use in the general population is so low, but its general psychopharmacological profile suggests that it lacks the abuse potential of amphetamines, cocaine, opiates or other widely abused substances. Indeed, accounts of any strong and sustained reinforcing effects of tryptamine compounds are rare in experimental literature. More typically, non-human animal studies conclude that administration of tryptamine derivatives such as mescaline, psilocybin or DMT result in erratic patterns of self-administration indicating that 'these compounds have weak reinforcing effects, or alternatively, mixed reinforcing and aversive effects' ([66], p. 156).

DISCUSSION

Any attempt to characterize the possible acute adverse health effects of ayahuasca is hampered by the very limited number of relevant scientific studies of DMT and β-carboline decoctions. This situation invites an easy commingling of facts, speculations, inferences, biases, conjectures and hidden agendas. Arguments made in the course of litigation are especially prone to linguistic obfuscation of empirical weaknesses. None the less, legal and policy decisions must be made in the light of what almost always seems to be insufficient evidence. Data available at this time indicate that the acute systemic toxicity of ayahuasca is, by comparison, substantially less than alcohol. The average acute lethal dose of ethyl alcohol is well-documented at approximately 330 g [67], 10 times the normal recreational dose. The acute lethal dose of ayahuasca was calculated in this review as 20 times the effective dose. This safety margin is similar to codeine, mescaline and methadone [9]. Previous estimates of the LD_{50} of DMT have been as high as 40 or 50 times the customary dose [9,68]; the difference is primarily a result of varying the safety factors that are used to extrapolate data from non-human laboratory animal studies to humans.

No acute health hazards, excluding potential serotonergic reactions, have been documented as a routine, serious threat from ayahuasca when ingested within the range of customary dosages. Possible chronic health effects of ayahuasca were not considered in the present paper.

Most public attention is focused on hazards that we want to avoid, such as accidents, heart attacks or bankruptcy. However, there are hazards that people accept, perhaps grudgingly, because they perceive a potential benefit—for instance, crossing a street against the traffic light, speeding to a hospital with a sick child, agreeing to an adjustable mortgage. Andritzky [69] has described the traditional use of ayahuasca in Amazonia during healing rituals. A more contemporary North American illustration was provided by a university administrator who reported that he previously considered Schedule I drugs to be a taboo option until he was diagnosed with metastatic liver cancer [70]. When potential benefits are considered, the option with the least risk is not necessarily the best choice.

Indeed, some risks are not merely accepted, but actively sought. Examples include hang-gliding, road racing and alcohol drinking contests. Recently, the internet has become a favored source of information for individuals seeking drug-related experiences. Boyer, Shannon & Hibberd [71] have profiled 12 adolescents in a drug treatment program who reported being influenced detrimentally by drug information, including a description of Syrian rue, that they found on the internet. However, the internet also contains descriptions of intoxicated misadventures that might serve as a cautionary tale (e.g. a self-reported ayahuasca overdose caused by the user's self-described 'swaggering arrogance' ([72], p. 1). Virtually all poisoning reports with tryptamine/MAOI mixtures involve individuals who prepared their own brew and/or who ingested an additional psychoactive substance [35,39,72,73].

The relative lack of abuse potential of ayahuasca in social settings seems very plausible. The unpredictable occurrence of frightening images and thoughts, plus predictable nausea and diarrhea, makes it a very unlikely candidate for a 'club drug'.

Finally, it might be noted that the discipline of toxicology has its own queasiness—especially about spiritual concepts such as 'transcendence', 'ineffability' and 'grace' that often appear in descriptions of ayahuasca sessions by physically and psychologically healthy individuals [74]. Many reported experiences are similar to descriptions of *samadhi* in advaitan Hinduism, *satori* in Zen Buddhism or *beatific vision* in Christianity. Such alleged beneficial experiences lie outside the pathology-oriented realm of toxicology, but not necessarily or completely beyond the scientific requirement of falsifiability. Variations in consciousness are, at least in theory, worthy of serious scientific study because of their central place in human endeavors.

Acknowledgements

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